

Pharmaceutical Composition

The present invention relates to a pharmaceutical composition. More particularly, it relates to an aerosol composition comprising a cannabinoid, to a metered dose
5 dispenser containing the composition and to a method of administering the composition to a patient.

Cannabis is known to be useful in therapy, for example in the treatment of nausea and vomiting associated with cancer chemotherapy, anorexia associated with AIDS, pain, epilepsy,
10 glaucoma, asthma and mood disorders. The principle active ingredient in cannabis is delta-9-tetrahydrocannabinol (delta-9-THC). A derivative of delta-9-THC, which possesses similar properties, is delta-8-tetrahydrocannabinol (delta-8-THC). Collectively, cannabis, delta-9-THC and derivatives thereof,
15 such as delta-8-THC, are known as cannabinoids.

International patent application publication number WO 01/66089 and United States patent application publication number 2002/0031480 disclose aerosol compositions comprising a cannabinoid and a propellant for administration to patients
20 using a metered dose dispenser. WO 03/006010, published on 23 January, 2003, also discloses aerosol compositions comprising a cannabinoid and a propellant for administration to patients using a metered dose dispenser.

It is reported in WO 01/66089 that administration of
25 aerosol compositions comprising the cannabinoid, delta-9-THC, and a propellant to the lungs of patients caused the patients to cough. Applicant has encountered a similar problem when administering aerosol formulations comprising delta-8-THC. This cough reaction is undesirable, because it results in
30 exhalation of much of the inhaled dose.

Surprisingly, it has now been found that by incorporating a sufficient amount of a certain kind of ingredient into the aerosol compositions, the cough reaction of patients is suppressed.

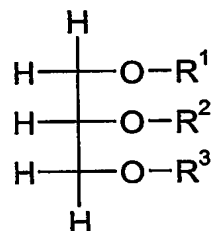
- 2 -

According to one aspect, therefore, the present invention provides a pharmaceutical composition for administration as an aerosol, which comprises a cannabinoid, a propellant and an effective amount of a cough suppressant.

5 Particularly good results have been obtained by incorporating medium chain triglycerides and propylene glycol diesters in a weight ratio of triglyceride to cannabinoid of at least 2:1, with the best results being obtained using weight ratios of at least 3:1 together with ethanol as a co-
10 solvent.

According to a preferred aspect, therefore the cough suppressant is a medium chain triglyceride or propylene glycol diester.

Medium chain triglycerides are well known in the
15 pharmaceutical formulation art, where they are mainly used in oral, parenteral and topical formulations. They are generally commercially available as mixtures of triglycerides of fatty acids consisting predominantly of octanoic (caprylic) and decanoic (capric) acid and may thus be represented by the
20 general formula



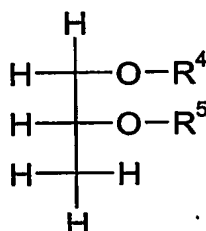
in which each of R^1 , R^2 and R^3 independently represents a group of formula $-\text{CO}-(\text{CH}_2)_n-\text{CH}_3$ in which n is an integer of from 6 to 8.

25 Examples of commercially available medium chain triglycerides are MIGLYOL™ 810 and 812, both caprylic/capric triglycerides available from CONDEA Chemie GmbH, Oleochemicals, Arthur-Imhausen-Str. 92, D-58433 Witten, Germany or CONDEA Vista Co., Commerce Dr., Cranford, NJ 07016,

- 3 -

United States, and CRODAMOL™ GTCC or CRODAMOL™ PC DAB 10(S), both caprylic/capric triglycerides, available from Croda Chemicals Ltd., Rawcliffe Bridge, Goole, East Riding, DN14 8PN.

- 5 Medium chain diesters of propylene glycol are generally commercially available as mixtures of diesters of fatty acids consisting predominantly of octanoic (caprylic) and decanoic (capric) acid and may thus be represented by the general formula



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in which each of R^4 and R^5 independently represents a group of formula $-\text{CO}-(\text{CH}_2)_n-\text{CH}_3$ in which n is an integer of from 6 to 8.

- 15 An example of a commercially available medium chain diester of propylene glycol is MIGLYOL™ 840, a propylene glycol dicaprylate/dicaprate, available from CONDEA Chemie GmbH, Oleochemicals, Arthur-Imhausen-Str. 92, D-58433 Witten, Germany or CONDEA Vista Co., Commerce Dr., Cranford, NJ 07016, United States.

- 20 The cough suppressant may conveniently be present in a weight ratio of cough suppressant to cannabinoid of from 2:1 to 25:1, preferably 2.5:1 to 15:1, most preferably 3:1 to 10:1.

The cannabinoid may be, for example, an extract of 25 natural cannabis, delta-9-THC, a derivative of delta-9-THC such as delta-8-THC, cannabidiol, or a mixture of any of these. Preferably it is delta-8-THC.

The propellant may be, for example, an alkane, such as butane, or a fluorocarbon, such as 1,1,1,2-tetrafluoroethane

- 4 -

(P-134a) or 1,1,1,2,3,3,3-heptafluoropropane (P-227).
Preferably it is P-134a.

The weight ratio of propellant to cannabinoid in the composition is conveniently in the range of from 10:1 to
5 10,000:1, such as from 250:1 to 10,000:1, preferably from 50:1 to 500:1.

The composition may further comprise one or more solid or liquid carriers or excipients, such as a pharmaceutically acceptable solvent, for example an alcohol such as ethanol, an
10 essential oil, such as peppermint, or a major component thereof, such as menthol, or a solid bulking agent, such as lactose. Preferably, the composition is a solution.

The one or more carriers or excipients in the aerosol composition may conveniently comprise from 0 to 25 % by weight
15 of the total composition.

It has been found to be advantageous to include ethanol in the composition. The ethanol may make up from 0.1% to 25% by weight of the formulation, preferably 1% to 25% of the formulation, more preferably 1% to 15%, most preferably from 3
20 to 5%. It has been found that when using high levels of ethanol, for example from 15 to 25% by weight, it is possible to use a lower ratio of cough suppressant to cannabinoid than is effective with low levels of ethanol. Furthermore, with high levels of ethanol, certain pharmaceutically acceptable
25 aerosol surfactants, such as isopropyl myristate and Brij 30 (a lauryl polyoxyethylene ether), can function as cough suppressants. However, the best results have been obtained using medium chain triglycerides and propylene glycol diesters in compositions containing from 3 to 5% by weight ethanol.

30 In certain cases, administration of the cannabinoid has been found to be associated with undesirable after effects, such as a burning or tingling sensation in the throat, or a dry throat. It has been found that these effects may be reduced or eliminated by incorporating an essential oil in the

- 5 -

composition. Examples of essential oils include peppermint (of which the major constituent is menthol), eucalyptus (of which the major constituent is cineole), aniseed and cajeput. According to a preferred aspect, therefore, the composition
5 according to the present invention may further comprise an essential oil, such as peppermint, eucalyptus, aniseed or cajeput, or a major component thereof, such as methanol or cineole. Particularly good results have been obtained by incorporating menthol in compositions. The essential oil (e.g.
10 menthol) preferably comprises from 0.02 to 0.1% by weight of the composition. The weight ratio of essential oil to delta-8-THC is preferably in the range of from 0.05:1 to 0.4:1, more preferably 0.1:1 to 0.3:1.

The pharmaceutical composition according to the invention
15 may conveniently be administered to a patient using a metered dose dispenser, such as a metered dose inhaler. According to another aspect, therefore, the present invention provides a metered dose dispenser containing a pharmaceutical composition according to the invention. Preferably the metered dose
20 dispenser is adapted to provide a unit dose containing from 0.05 to 0.5 mg of the cannabinoid, preferably from 0.1 to 0.2 mg.

According to another aspect, the present invention provides a method of administering an aerosol composition
25 comprising a cannabinoid and a propellant to a patient, which comprises administering the cannabinoid and propellant with an effective amount of a cough suppressant.

According to another aspect, the present invention provides the use of an effective amount of a cough suppressant
30 in the manufacture of a medicament for suppressing coughing when an aerosol composition comprising a cannabinoid and a propellant is administered to a patient.

As used herein, the term patient refers to any human or non-human animal. Preferably the patient is a human.

- 6 -

The aerosol composition is conveniently administered by inhalation. However, it may be administered via a pulmonary, sub-lingual, nasal or buccal route. Thus, although the risk of provoking a cough is lower if an aerosol lacking a cough suppressant is administered via a sub-lingual, nasal or buccal route, it would be advantageous for patients to receive cannabinoid with a cough suppressant, in accordance with the present invention.

The following Examples illustrate the invention.

- 7 -

Example 1

	Ingredient	Weight in mg
	delta-8-THC	5.2 (0.1 mg dose)
	P-134a	1606
5	Crodamol GTCC	15.9 (3.1:1 cough suppressant:cannabinoid)
	Ethanol	42.7 (2.6% by weight)

Comparison Example 1

	Ingredient	Weight in mg
10	delta-8-THC	6.1 (0.12 mg)
	P-134a	1477
	Crodamol GTCC	11.4 (1.9:1)
	Ethanol	50.1 (3.3%)

- 15 Notes: A comparison between Example 1 and Comparison Example 1 shows that having a sufficient amount of Crodamol GTCC in the aerosol composition is important.

Example 2

20	Ingredient	Weight in mg
	delta-8-THC	5.0 (0.12 mg)
	P-134a	1220
	Crodamol PC DAB 10(S)	52 (10.4:1)
	Ethanol	0 (0%)

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Example 3

	Ingredient	Weight in mg
	delta-8-THC	5.0 (0.23 mg)
	P-134a	656
30	Crodamol PC DAB 10(S)	15.5 (3.1:1)
	Ethanol	49 (7%)

- 8 -

Example 4

	Ingredient	Weight in mg
	delta-8-THC	5.1 (0.12 mg)
	P-134a	1288
5	Crodamol PC DAB 10(S)	15.1 (3:1)
	Ethanol	100 (7.2%)

Example 5

	Ingredient	Weight in mg
10	delta-8-THC	5.1 (0.12 mg)
	P-134a	1274
	Crodamol PC DAB 10(S)	15.2 (3:1)
	Ethanol	45.9 (3.5%)

Example 6

	Ingredient	Weight in mg
	delta-8-THC	5.2 (0.12 mg)
	P-134a	1301
	Crodamol PC DAB 10(S)	16.8 (3.2:1)
20	Ethanol	144.3 (10%)

Example 7

	Ingredient	Weight in mg
	delta-8-THC	6 (0.15 mg)
25	P-134a	1128
	Crodamol PC DAB 10(S)	51 (8.5:1)
	Ethanol	64 (5.4%)

Example 8

	Ingredient	Weight in mg
30	delta-8-THC	10 (0.52 mg)
	P-134a	581
	Crodamol PC DAB 10(S)	105 (10.5:1)
	Ethanol	0 (0%)

- 9 -

Example 9

Ingredient	Weight in mg
delta-8-THC	20 (0.22 mg)
P-134a	2689
5 Crodamol PC DAB 10(S)	300 (15:1)
Ethanol	0 (0%)

Comparison Example 2

Ingredient	Weight in mg
10 delta-8-THC	5 (0.24 mg)
P-134a	634
Crodamol PC DAB 10(S)	5.5 (1.1:1)
Ethanol	49 (7.2%)

15 Comparison Example 3

Ingredient	Weight in mg
delta-8-THC	5.5 (0.13 mg)
P-134a	1253
Crodamol PC DAB 10(S)	13.5 (2.5:1)
20 Ethanol	101 (7.5%)

Example 10

Ingredient	Weight in mg
delta-8-THC	10 (0.19 mg)
25 P-134a	1340
Crodamol PC DAB 10(S)	58 (6.8:1)
Ethanol	151 (10.1%)
Micronized lactose	10

30 Example 11

Ingredient	Weight in mg
delta-8-THC	5.1 (0.12 mg)
P-134a	1239
Miglyol 810	17.7 (3.5:1)
35 Ethanol	49.2 (3.8%)

- 10 -

Example 12

	Ingredient	Weight in mg
	delta-8-THC	5.4 (0.09 mg)
5	P-134a	1796
	Miglyol 812	18 (3.3:1)
	Ethanol	41.1 (2.2%)

Example 13

	Ingredient	Weight in mg
10	delta-8-THC	10 (0.09 mg)
	P-134a	3207
	Miglyol 812	20.8 (2.1:1)
	Ethanol	193.4 (5.7%)

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Example 14

	Ingredient	Weight in mg
	delta-8-THC	10 (0.1 mg)
	P-134a	3062
20	Miglyol 812	20.3 (2:1)
	Ethanol	261.5 (7.9%)

Comparison Example 4

	Ingredient	Weight in mg
25	delta-8-THC	5.6 (0.09 mg)
	P-134a	1788
	Miglyol 812	12.3 (2.2:1)
	Ethanol	41.9 (2.3%)

30 Comparison Example 5

	Ingredient	Weight in mg
	delta-8-THC	10.3 (0.1 mg)
	P-134a	3019
	Miglyol 840	20.8 (2:1)
35	Ethanol	124.7 (4%)

Notes: A comparison between Examples 13 and 14 and Comparison Examples 4 and 5 shows that increasing the percentage by weight of ethanol can compensate for a reduced cough suppressant/cannabinoid ratio.

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Example 15

Ingredient	Weight in mg
delta-8-THC	25 (0.2 mg)
P-134a	3451
10 Miglyol 812	75 (3:1)
Ethanol	145 (4%)

Example 16

Ingredient	Weight in mg
15 delta-8-THC	52.4 (0.2 mg)
P-134a	6952
Miglyol 812	132.4 (2.5:1)
Ethanol	597.9 (7.9%)

20 **Example 17**

Ingredient	Weight in mg
delta-8-THC	6.6 (0.14 mg)
P-134a	1423
Miglyol 840	17.1 (2.6:1)
25 Ethanol	48.6 (3.3%)

Comparison Example 6

Ingredient	Weight in mg
delta-8-THC	4.97 (0.1 mg)
30 P-134a	1137
Ethanol	274.2 (19.4%)

- 12 -

Example 18

	Ingredient	Weight in mg
	delta-8-THC	25.4 (0.20 mg)
	P-134a	3568
5	Miglyol 840	77.8 (3.1:1)
	Ethanol	146.18 (3.9%)
	Eucalyptus Oil	2.7 (0.07%)

Example 19

	Ingredient	Weight in mg
	delta-8-THC	24.8 (0.20 mg)
	P-134a	3509
	Miglyol 840	78.4 (3.1:1)
	Ethanol	148.35 (4.1%)
15	Peppermint Oil	2.7 (0.07%)

Example 20

	Ingredient	Weight in mg
	delta-8-THC	12.46 (0.10 mg)
20	P-134a	3500
	Miglyol 840	44.2 (3.5:1)
	Ethanol	145 (4.0%)
	Menthol	1.3 (0.04%, menthol: delta 8 0.1:1)

25 Example 21

	Ingredient	Weight in mg
	delta-8-THC	5.0 (0.10 mg)
	P-134a	1380
	Miglyol 840	14.1 (2.8:1)
30	Ethanol	63.2 (4.4%)
	Menthol	0.69 (0.05%, 0.14:1)

- 13 -

Example 22

	Ingredient	Weight in mg
	delta-8-THC	2.6 (0.04 mg)
	P-134a	1861
5	Miglyol 840	7.53 (2.9:1)
	Ethanol	62.7 (3.3%)
	Menthol	0.36 (0.02%, 0.14:1)

Example 23

	Ingredient	Weight in mg
	delta-8-THC	2.62 (0.05 mg)
	P-134a	1512
	Miglyol 840	8.08 (3.1:1)
	Ethanol	62.1 (3.9%)
15	Menthol	0.71 (0.04%, 0.27:1)

Example 24

	Ingredient	Weight in mg
	delta-8-THC	5 (0.11 mg)
20	P-134a	990
	Brij™ 30	28 (5.5:1)
	Ethanol	249 (20%)

Example 25

	Ingredient	Weight in mg
25	delta-8-THC	6 (0.12 mg)
	P-134a	1068
	Isopropyl myristate	31 (5:1)
	Ethanol	271 (20%)

- 14 -

Example 26

Ingredient	Weight in mg
delta-8-THC	12 (0.1 mg/dose)
P-134a	3430
5 Miglyol 812	36 (3:1)
L-Menthol	1.51
Ethanol	302 (8%)

Example 27

10	Ingredient	Weight in mg
	delta-9-THC	4.99
	P-134a	1514.9
	Miglyol 812	17.38
	Ethanol	63.7

15

Example 28

	Ingredient	Weight in mg
	Cannabidiol	11.9
	P-134a	1814.0
20	Miglyol 812	30.3
	Ethanol	130.3

The effect of administering the compositions of the Examples and Comparison Examples on patients was investigated as follows:-

The ingredients were filled in standard glass vials with a normal valve and seals. The completed units were put in a standard actuator and primed. Then one puff of each was taken in the normal manner by the volunteer.

The compositions of the Examples were found to produce no cough, whereas those of the Comparison Examples were found to produce a spontaneous cough within 2-3 seconds.

An experiment was also conducted to investigate whether the cough suppressant and cannabinoid could be administered sequentially. This is described below.

5

	First Dose	Second Dose
Ingredient	Weight in mg	Weight in mg
delta-8-THC	0	4.8 (0.01mg)
P-134a	1540.4	1502.0
10 Miglyol 812	25.2	
Ethanol	65.4 (4.1%)	62.3 (4.0%)
Eucalyptus Oil	0	18.6

The first dose, containing Miglyol 812, was inhaled twice,
15 then the second dose was inhaled. The ratio of Miglyol 812:
delta-8-THC inhaled was 10.5:1. A spontaneous cough was
provoked after 5 seconds. This experiment shows that the
cough suppressant needs to be administered with the
cannabinoid.

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It will be understood that the Examples have been provided to
illustrate the invention. The invention is not limited to
compositions using the particular cough suppressants described
in these Examples or particularly described herein. Following
25 the teachings herein about how the cough reflex may be
suppressed in aerosol formulations containing a cannabinoid
and a propellant, those skilled in the art should readily be
able to identify other cough suppressants.